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Neuro-Oncology

Emerging Immunotherapies in the Treatment of Brain Metastases

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Brain metastasis • Immunotherapy

Abstract

Brain metastases account for considerable morbidity and mortality in patients with cancer. Despite increasing prevalence, limited therapeutic options exist. Recent advances in our understanding of the molecular and cellular underpinnings of the tumor immune microenvironment and the immune evasive mechanisms employed by tumor cells have shed light on how immunotherapies may provide therapeutic benefit to patients. The development and evolution of immunotherapy continue to show promise for the treatment of brain metastases. Positive outcomes have been observed in several studies evaluating the efficacy and safety of these treatments. However, many challenges persist in the application of immunotherapies to brain metastases. This review discusses the potential benefits and challenges in the development and use of checkpoint inhibitors, chimeric antigen receptor T-cell therapy, and oncolytic viruses for the treatment of brain metastases. Future studies are necessary to further evaluate and assess the potential use of each of these therapies in this setting. As we gain more knowledge regarding the role immunotherapies may play in the treatment of brain metastases, it is important to consider how these treatments may guide clinical decision making for clinicians and the impact they may have on patients. ***The Oncologist*** 2021;26:231–241

Implications for Practice: Immunotherapies have produced clinically significant outcomes in early clinical trials evaluating patients with brain metastases or demonstrated promising results in preclinical models. Checkpoint inhibitors have been the most common immunotherapy studied to date in the setting of brain metastases, but novel approaches that can harness the immune system to contain and eliminate cancer cells are currently under investigation and may soon become more common in the clinical setting. An understanding of these evolving therapies may be useful in determining how the future management and treatment of brain metastases among patients with cancer will continue to advance.

Introduction

Brain metastases remain a serious complication of cancer. Malignancies that spread to the central nervous system (CNS) are associated with significant mortality, with a 2-year survival rate of 8.1% and a 5-year survival rate of 2.4% across all primary tumor types for metastatic brain cancer [1]. Neurological disease is the cause of death for more than 50% of these patients [2, 3]. Morbidity associated with brain metastasis is another serious concern, as quality of life is markedly reduced among patients with brain tumors [4]. Studies suggest that brain metastasis will occur in approximately 20% of all individuals diagnosed with cancer [5–7]. Autopsy studies estimate the incidence of CNS involvement at 40% to 75% at the time of death depending on the primary cancer type [8–11].

All cancer types can develop the ability to spread to the brain, with lung, breast, and melanoma being the most common among adults [5, 12]. Of note, the prevalence of brain metastases for adult patients with renal cell carcinoma and colorectal cancer has increased significantly in recent years, likely because of advances in the treatment

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and diagnosis of cancer overall [13]. The total number of people known to be living with metastatic brain cancer is expected to rise as patient survival increases and our ability to detect and control metastases in other organs improves. This makes the study of brain metastases vital in the prevention of future morbidity and mortality associated with cancer.

Despite the increasing prevalence of brain metastasis among patients with cancer, limited treatment options currently exist [14]. Among the most promising strategies in the treatment and management of brain tumors is the use of immunotherapy to enhance the immune system to specifically attack cancerous cells [15]. Although the CNS was previously considered an immune-privileged environment, metastases to the CNS are now viewed as potential targets for a number of immunotherapeutic drugs. The earliest evidence regarding the potential use of immunotherapy for secondary brain tumors existed as early as the 1990s when clinical trials reported intracranial responses to high-dose interleukin-2 therapy delivered intravenously in patients with metastatic melanoma [16]. However, despite these responses, clinical trials investigating immunotherapeutic agents for metastatic cancers traditionally excluded individuals with brain metastasis because of concerns that inflammatory responses might lead to neurological complications.

As the understanding of the tumor immune microenvironment has grown and the mechanisms by which tumor cells evade the immune system become known, more effective therapies have been developed. These treatments tend to inhibit critical immune checkpoints, thereby relieving regulatory pressure preventing antitumor immunity and can lead to remarkable extracranial and intracranial responses. This review covers the most recent advances and growing challenges in the field of immunotherapy relevant to the treatment of brain metastases. Current progress of immune checkpoint inhibitors in clinical trials, as well as the investigation of chimeric antigen receptor (CAR) T-cell therapy in solid brain tumors, and the possible role of oncolytic viruses as an adjuvant in combination with immunotherapy will be summarized. Several key trials evaluating immunotherapy in the setting of brain metastases are outlined in Table 1. The hope is that enhancing antitumor immune responses with immunotherapy will help reduce morbidity and mortality associated with brain metastases. Meanwhile, local therapies such as stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), and neurosurgery remain the pillars for treatment of brain metastases, and it will be important to carefully consider the potential benefits and challenges for each of these alternatives individually as new therapeutic agents and modalities continue to emerge and evolve.

Recent Advances and Ongoing Challenges of Checkpoint Inhibitors

The number of patients with brain metastases eligible for, and deriving benefit from, immunotherapy using checkpoint inhibitors has risen dramatically in the last few years [17]. An initial 2010 study [18] of 676 individuals with previously treated metastatic melanoma—which allowed enrollment of 82 patients with treated central nervous system metastases—was the first to demonstrate that treatment with ipilimumab, a human monoclonal antibody against cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), improved survival. Given the high rates of brain metastases in melanoma and the limited systematic therapy options, this finding naturally led to further investigations of various checkpoint inhibitors specifically evaluating brain metastases, first in the setting of melanoma [19] and later in lung [20], with similar observed clinical outcomes (Table 1).

In addition to antibodies against CTLA-4, human monoclonal antibodies targeting programmed cell death protein 1 (PD-1) receptor, such as pembrolizumab and nivolumab, have been evaluated for efficacy in patients with brain metastasis. These antibodies block PD-1 binding to its ligands programmed death-ligand (PD-L) 1 and PD-L2, which are often upregulated on tumor cells and in the tumor microenvironment, where they suppress T-cell responses [21]. Most recently, trials have begun actively looking at the safety and efficacy of checkpoint inhibitor combinations for treating brain metastases [22, 23]. An overview of the mechanism of checkpoint inhibitors is presented in Figure 1.

Evidence from Clinical Trials

In 2015, results of an ongoing trial investigating pembrolizumab that ultimately enrolled 36 neurologically asymptomatic patients aged 18 years or older with untreated brain metastasis that had at least one mass measuring 5 to 20 mm were first reported at the American Society of Clinical Oncology annual conference providing supporting evidence for increased responses, stable disease, and improved overall survival in a 6-month period for patients with melanoma and for patients with non-small cell lung cancer [20, 24, 25]. Goldberg et al. reported the results of a phase II nonrandomized open-label clinical trial evaluating long-term outcomes of pembrolizumab treatment among a total of 42 neurologically asymptomatic patients aged 18 years or older with stage IV non-small cell lung cancer, a minimum life expectancy of 3 months, and at least one brain metastasis measuring 5 to 20 mm that was untreated or continued to progress despite local therapy [26]. In this study, patients with brain metastases were treated with pembrolizumab intravenously every 2 weeks with cohorts divided into less than 1% PD-L1 expression or at least 1% PD-L1 expression. After a median follow-up of 8.3 months, responses were observed only in patients with 1% or more expression of PD-L1. Of the 37 patients in this cohort, 29.7% had a brain metastases response (seven had partial responses, and four had complete responses). Furthermore, the 2-year overall survival among these patients was 34% (compared with 14.3% seen in previous observational studies) [27].

In 2018, a multicenter open-label phase II randomized clinical trial evaluated nivolumab and ipilimumab among 79 patients with histologically confirmed stage IV melanoma and at least one brain metastasis measuring 5 to 40 mm: cohort A included 36 participants with asymptomatic brain metastases with no prior local therapy (such as neurosurgery, SRS, or WBRT) who received nivolumab with

Table 1. Key investigations evaluating the potential of immunotherapy in brain metastases

Primary tumor	Year published	Study type	Intervention	Total no. of participants[a]	Outcome	Key takeaways
Melanoma	1999 [17]	Retrospective analysis of eight trials conducted from 1985 to 1993	IL-2	270	OR: 16%; PR: 10% Median duration for OR: not achieved Median duration for PR: 5.9 months	Intracranial responses to high-dose therapy observed among patients
Melanoma	2010 [19]	Randomized, double-blind, phase III trial	Ipilimumab	676	Median OS: 10.1 months	Improved overall survival
Melanoma	2012 [20]	Non-randomized, open-label, phase II trial	Ipilimumab	72	12-week disease control: 24% of neurologically asymptomatic patients	Activity in some patients, particularly when metastases are small and asymptomatic; no unexpected toxicities
Melanoma	2015 [26]	Non-randomized, open-label phase II trial	Pembrolizumab	17	PR: 25% (3/12 of evaluable patients); stable disease: 17% (2/12)	Early results suggest promising activity in untreated brain metastases
Melanoma	2018 [23]	Randomized, open-label, phase II trial	Nivolumab, Ipilimumab	79	OR: 46% (nivolumab plus ipilimumab); 20% (nivolumab alone) CR: 17% (nivolumab plus ipilimumab), 12% (nivolumab alone)	Combination therapy displays intracranial response; suggested as first-line therapy
Melanoma	2018 [24]	Open-label, single-group, phase II trial	Nivolumab, Ipilimumab	94	CR: 26%; PR: 30%; stable disease for at least 6 months: 2%	Combination therapy has clinically meaningful efficacy concordant with extracranial activity in untreated brain metastases
Melanoma	2019 [37]	Single-site retrospective analysis	Temporal relationship of surgery and immunotherapy	142	Median survival: 22.7 months (surgery followed by immunotherapy) and 10.8 months (immunotherapy alone)	Early surgical resection for local control before commencing immunotherapy may improve patient outcomes
Melanoma, colorectal cancer[b]	2018 [97]	Randomized, double-blind, phase I	Reovirus	9[b]	No change in expected survival	Intravenous reovirus selectively gains access to brain tumors in xenograft murine models and in a small number of patients
Melanoma, NSCLC	2016 [21]	Non-randomized, open-label, phase II trial	Pembrolizumab	36	OR: 22% in melanoma; OR: 33% in NSCLC	Activity in some patients with an acceptable safety profile; possible role for systemic immunotherapy
NSCLC	2015 [25]	Non-randomized, open-label, phase II trial	Pembrolizumab	10	OR: 44% (4/9 evaluable patients)	Early results suggest promising activity in untreated brain metastases

[a]Total number of participants at time of cited publication; some investigations presented early results as part of ongoing trials.
[b]This particular study implanted intracranial malignant melanoma in immunocompetent mice. In addition, nine patients were recruited with varying brain tumor histology (two with melanoma, one with colorectal cancer, and six with high-grade glioma).
Abbreviations: CR, complete response; IL-2, interleukin-2; NSCLC, non-small cell lung cancer; OR, overall response; OS, overall survival; PR, partial response.

ipilimumab; cohort B included 27 participants with asymptomatic brain metastases with no prior local therapy who received nivolumab; and cohort C included 16 participants who had failed local therapy, presented with neurological symptoms, or developed leptomeningeal disease who received nivolumab. The results of the study showed that combination therapy using nivolumab with ipilimumab achieved higher intracranial responses in cohort A (46%) than monotherapy in cohort B (20%) or cohort C (6%) and was therefore suggested as first-line therapy for patients with neurologically asymptomatic, untreated brain metastases [22]. A contemporary study by Tawbi et al. evaluated

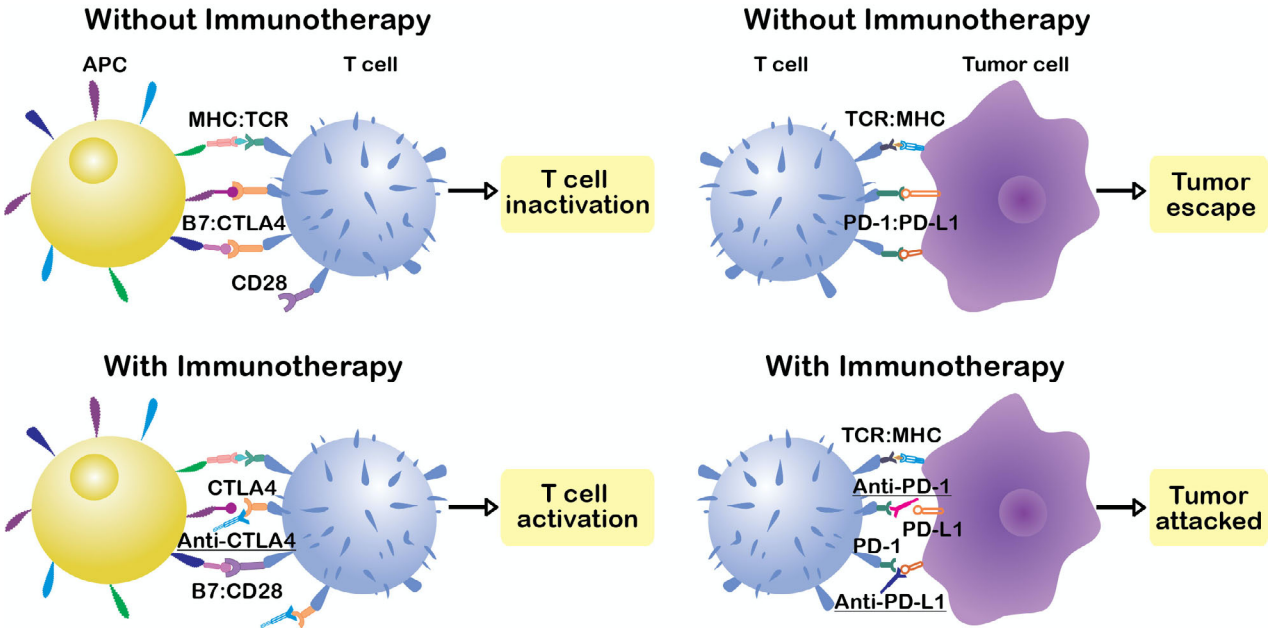

Figure 1. Immune checkpoint blockade for cancer immunotherapy. Checkpoint inhibitors are a class of immunotherapy drugs. Immune checkpoints normally function to prevent an immune response from overwhelming or attacking the host. These checkpoints are activated when T cells recognize and bind to proteins, also known as "checkpoints," that they recognize on other cells such as antigen-presenting cells, which in turn generate an "off" signal in the T cell. Well-known protein pairings include B7 with CTLA-4 and CD28, and PD-1 with PD-L1 and PD-L2. Unfortunately, tumor cells can coopt this system by presenting checkpoints such as PD-L1, allowing them to escape T-cell–mediated immunity. Checkpoint inhibitors block the binding of T cells to checkpoint proteins, preventing the negative regulation of T-cell responses and subsequently allowing the T cell to attack and destroy tumor cells. Abbreviations: APC, antigen-presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor.

this same combination in 94 neurologically asymptomatic patients with histologically confirmed melanoma and at least one brain metastasis measuring 5 to 30 mm that had not been previously irradiated or that required immediate intervention such as with neurosurgery or SRS as part of a single-arm phase II clinical trial. A total of 94 patients with asymptomatic CNS disease and previously untreated received combination therapy in a similar fashion with nivolumab plus ipilimumab every 3 weeks for up to four doses followed by nivolumab every 2 weeks. In this group, intracranial response was observed in 57% of patients [23]. Antibodies that directly bind to and inhibit PD-L1, such as atezolizumab, avelumab, and durvalumab, are similarly being evaluated. Efficacy and toxicity profiles of the various inhibitors targeting the PD-1–PD-L1/PD-L2 interaction can differ between cancer types, rationalizing the need for multiple drugs with similar mechanisms of action [28]. Several more trials are underway to expand the use of checkpoint inhibitors to CNS metastases originating from various primary sites (NCT02886585, NCT02939300). These and other ongoing trials using immunotherapy in the setting of brain metastases are outlined in Table 2.

Improving Therapy with Combinations

Among the purported benefits of checkpoint inhibitors is their ability to overcome immune resistance in tumors without the toxicity commonly associated with chemotherapy [28]. However, the microenvironment of solid tumors can thwart immune responses by impeding infiltration of immune cells into the tumor, contributing to the variability in responses seen among patients [29]. Therapies that can increase immune infiltration of tumors are therefore being evaluated in combination with checkpoint inhibitors. This includes radiotherapy, the immunomodulatory effects of which were first noted over 100 years ago [30] and have now been described in detail for use against metastatic brain cancers [31]. Similarly, there is evidence that antiangiogenic agents such as bevacizumab can also reprogram the tumor microenvironment to be more immune permissive [32–34]. For example, studies have shown that pharmacological blockade of VEGF increases cluster of differentiation (CD) 8+ T-cell response in solid tumor models [33]. Also, VEGF found in the tumor microenvironment enhances expression of inhibitory checkpoints, including PD-1, which can be reverted using antiangiogenic agents in animal models [35]. Clinical trials investigating whether these interventions can sensitize CNS metastases to checkpoint blockade are found in Table 2.

Moreover, in patients with melanoma brain metastases, upfront surgery to reduce tumor burden prior to treatment with checkpoint inhibitors has been linked to better clinical outcomes [36] again elucidating how different combination therapies may obtain superior results.

Biomarkers

Multiple biomarkers have been proposed to identify which patients may derive clinical benefit from immune checkpoint blockade in the setting of cancer. These biomarkers assessing response in immune checkpoint

Table 2. Key clinical trials underway evaluating immunotherapy in brain metastases

Primary tumor	Intervention	Title	Stage	Trial number	Study completion date
Solid tumors	Personalized cellular vaccine	Personalized Cellular Vaccine for Brain Metastases (PERCELLVAC3)	Phase I	NCT02808416	09/2020
Breast cancer	DV, allogeneic HSCs, CTLs DV, autologous HSCs, CTLs	Proteome-Based Immunotherapy of Brain Metastases from Breast Cancer	Phase II	NCT01782274	12/2020
Breast cancer	Atezolizumab, stereotactic radiosurgery	Atezolizumab + Stereotactic Radiation in Triple-Negative Breast Cancer and Brain Metastasis	Phase II	NCT03483012	09/2025
Breast and lung cancer	DCVax-Direct	Dendritic Cell Therapy for Brain Metastases from Breast or Lung Cancer	Phase I	NCT03638765	12/2020
Lung cancer	DV, allogeneic HSCs, CTLs DV, autologous HSCs, CTLs	Proteome-Based Immunotherapy of Lung Cancer Brain Metastases	Phase II	NCT01782287	12/2020
Melanoma, NSCLC	Pembrolizumab, bevacizumab	Pembrolizumab Plus Bevacizumab for Treatment of Brain Metastases in Metastatic Melanoma or Non-Small Cell Lung Cancer	Phase II	NCT02681549	05/2024
Melanoma, untreated and progressive metastases	Pembrolizumab, stereotactic radiosurgery	Pembrolizumab in Central Nervous System Metastases	Phase II	NCT02886585	01/2024
Melanoma	Atezolizumab, bevacizumab, cobimetinib	Bevacizumab and Atezolizumab with or Without Cobimetinib in Treating Patients with Untreated Melanoma Brain Metastases	Phase II	NCT03175432	06/2021
Melanoma	Ipilimumab, nivolumab, stereotactic radiotherapy	Anti-PD 1 Brain Collaboration + Radiotherapy Extension (ABC-X Study)	Phase II	NCT03340129	08/2024
Melanoma	Pembrolizumab, ipilimumab, nivolumab, encorafenib, binimetinib, dabrafenib, trametinib	Melanoma Metastasized to the Brain and Steroids (MEMBRAINS)	Phase II	NCT03563729	06/2025
HER2+ tumors	CAR T-cell therapy	HER2-CAR T Cells in Treating Patients with Recurrent Brain or Leptomeningeal Metastases	Phase I	NCT03696030	08/2021

Abbreviations: CAR, chimeric antigen receptor; CTL, cytotoxic lymphocyte; DV, dendritic vaccine; HSC, hematopoietic stem cell; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1.

blockage include neoantigen expression [37], mutational load [38], expression of immune checkpoint receptor ligand [39], and immune cell infiltration [40]. It has been shown that despite statistically significant benefit from checkpoint inhibitors in phase I/II trials, results from phase III trials may differ using predefined biomarkers [41]. Additionally, cancer trials with non-CNS involvement have shown that specific expression of an eight-gene cluster is associated with poor response to anti–CTLA-4 and may be predictive of overall survival [42]. Because of the complexities of biomarkers and its dependence on the interactions present in the tumor microenvironment it has been suggested that dynamic biomarkers, which depend on the therapeutic response, may ultimately be necessary to successfully predict outcomes to immune checkpoint blockage in patients with cancer [43].

Biomarkers and their relationship to checkpoint blockade response have also been evaluated in brain metastases. Tumor properties such as PD-L1 expression have been evaluated to estimate efficacy. In the study by Tawbi et al., tumor PD-L1 expression of 5% or more was associated with greater clinical benefit using combination therapy (nivolumab and ipilimumab) when compared with patients who had lower than 5% tumor PD-L1 expression [23]. Similarly, Long et al. described increased intracranial progression-free survival using combination therapy for patients with high baseline PD-L1 expression (≥1%) compared with monotherapy [22]. Other nontumor properties

that have also been examined in the efficacy of immune checkpoint blockade include lactate dehydrogenase, C-reactive protein, human leukocyte antigen class I genotype, cytokine levels, lymphocyte count, and the gut microbiome [44, 45].

The mutational burden of tumors, which differs across cancer types and even between tumors of the same histology, is likely to play a role in clinical responses observed [46]. Genetic mutations that affect protein sequences give rise to neoantigens that can be recognized as nonself and thus mark the tumor cells as targets for immune clearance. The mutational burden in tumors has been linked to their neoantigen load, as well as response to immunotherapy [47]. This will be an important consideration for brain metastases, which differ from their primary tumors in the mutations they carry, and presumably the neoantigens they express, because of branched evolution [48]. Given current understanding, multiple biomarkers will likely be necessary to develop a model that can predict clinical response to therapy using checkpoint inhibitors [45].

Imaging and Early Diagnosis

The present-day gold standard for detection of brain metastases relies on magnetic resonance imaging (MRI) that may not be sensitive enough to detect very early metastases. Brain lesions may therefore be detected only once they have established a microenvironment supportive of tumor growth and proliferated enough to be visible using MRI or computed tomography scans. Alternative approaches that can enable earlier diagnoses of brain metastases are thus being explored that may circumvent the need for invasive surgery. An earlier diagnosis could lead to improved clinical benefits of immune checkpoint inhibitors as baseline tumor size prior to treatment is negatively associated with efficacy of immune checkpoint inhibitors [49, 50].

Remaining Challenges

With the rise of checkpoint inhibitors, some concerns have emerged. Tumor inflammation and pseudoprogression commonly observed in imaging can lead to additional symptoms and make assessment of tumor growth difficult [51]. Side effects have been observed, although notably, trials investigating brain metastases have not shown higher rates of toxicities or neurologic adverse events compared with extracranial metastases [52]. Rare but fatal complications have been reported, especially when used in combination, as in the case of immunotherapy-related myocarditis [53]. Other known immunotherapy-related adverse events associated with checkpoint inhibitors include dermatitis (with all-grade incidence of 17%), endocrinopathies (10%), colitis (2%), hepatitis (3%), and pneumonitis (3%) [18, 52, 54–56]. Neurologic toxicities from checkpoint inhibitors, with an incidence of 1% to 2%, include CNS paraneoplastic syndromes, encephalitis, multiple sclerosis, and hypophysitis [52, 57]. Aside from its potential side effects, the ability to successfully target brain metastases only among certain patients, such as those expressing high levels of PD-L1, indicates another potential limitation of checkpoint inhibitors [45]. This translates to a significant number of patients that may ultimately have little to no clinical benefit from current checkpoint inhibition therapy therefore necessitating other forms of treatment. Additional studies will be necessary to explore some of these challenges and determine how the tumor microenvironment can be overcome to more successfully target tumor cells in the brain.

CAR T-Cell Therapy for Solid Brain Lesions

The use of CAR T cells through adoptive T-cell transfer is the leading candidate for immunotherapy in hematologic malignancies. CAR T-cell targeting of CD19 has exhibited striking efficacy in the treatment for several of these cancer types and its expansion to brain metastases is now being explored [58, 59]. In the 1980s, Kuwana et al. [60] and Gross et al. [61] were the first to report antigen recognition using CAR T cells. Since then, the potential of CAR T-cell therapy has been widely recognized and continues to show great promise in cancer treatment, with continued potential for patients with metastatic brain lesions. Initial successes in CAR T-cell therapy targeting CD19 led to the first gene therapy approval for acute lymphoblastic leukemia (ALL) by the U.S. Food and Drug Administration (FDA) [62]. Studies of CAR T-cell therapy targeting B-cell maturation antigen and CD22 have reported similar activity against both multiple myeloma [63] and ALL [64]. It has been used successfully in follicular lymphoma [65] and chronic lymphocytic leukemia [66], and several early trials have shown promising results in the treatment of solid tumors, including in patients with neuroblastoma [67] and sarcoma [68], serving as a guide toward the treatment of brain metastases in the future. Some success has also been achieved in the treatment of glioblastoma, further highlighting the potential of CAR T-cell therapy in intracranial tumors such as brain metastases. The mechanism of CAR T-cell therapy is presented in Figure 2.

Looking Toward CAR T-Cell Therapy for Brain Metastases

Although hematologic malignancies have displayed positive results, solid tumors such as brain metastases remain a challenge. Researchers have attempted to outline the road toward effective therapy by focusing on potential antigens found in solid tumors [69, 70], but concerns remain. Previous CAR T-cell therapy targeting solid tumors have had mixed results. In 2010, CAR T-cell therapy targeting ERBB2/HER2 resulted in the death of the first treated patient because of low levels of ERBB2/HER2 expressed in the lungs which led to pulmonary failure and increase in serum markers associated with cytokine storm [71]. However, a later trial using lower affinity CAR T cells targeting ERBB2/HER2 showed beneficial antitumor effects in patients with HER2-positive sarcomas [68], illustrating the potential for effective therapy in solid tumors.

The use of CAR T-cell therapy for neural and brain tumors has achieved similar outcomes as solid tumors of nonneural origin. In 2018, CAR T-cell therapy directed at neuroblastoma resulted in induced fatal encephalitis [72]. However, another trial by Brown et al. involving direct infusion into the resected tumor cavity of patients with glioblastoma showed positive results [73], paving the way for

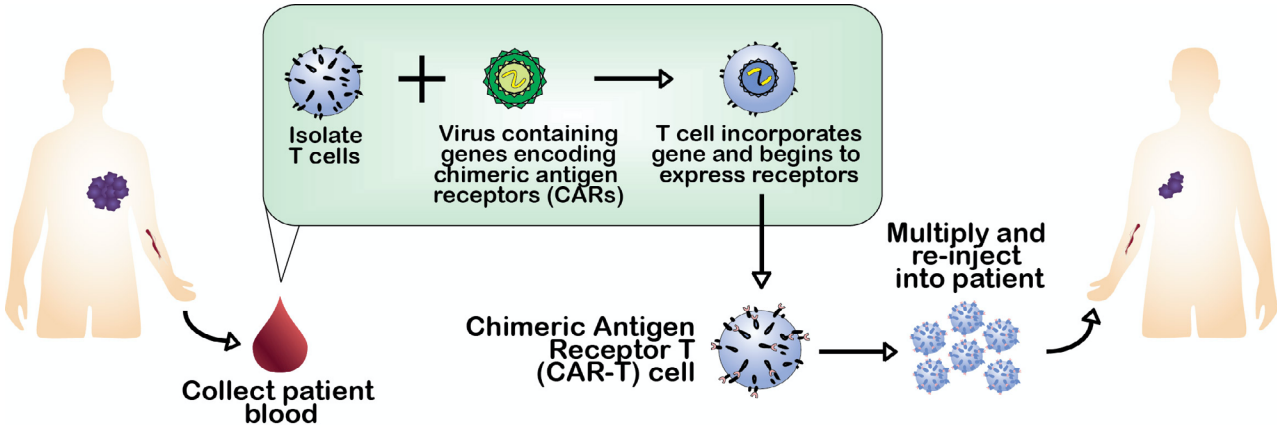

Figure 2. CAR T-cell therapy in cancer. In CAR T-cell therapy, the T cells are isolated, and the remainder of the blood is returned to the body. These T cells, the primary killing cells of the adaptive immune system, are unable to recognize the cancer cells or fully destroy them. The isolated T cells are then genetically altered using viral vectors carrying genes encoding CARs that are subsequently expressed on the surface of modified T cells. These receptors allow the T cells to recognize and respond to the tumor cells, and these newly engineered CAR T cells are then multiplied to make millions of copies and reintroduced into the patient. There, CAR T cells continue to multiply, recognize and attach to specific antigens presented on the tumor cells to become activated, and proceed to kill the tumor cell. The CAR T cells remain in the body for a prolonged period to aid in destroying any remaining or new tumor cells that arise, allowing the patient to remain in remission.
Abbreviation: CAR, chimeric antigen receptor.

how CAR T-cell therapy may be useful for lesions in the brain [73, 74]. Additional investigations using human xenograft mouse models has shown that CAR T-cell therapy may effectively target HER2-positive brain metastases in patients with breast cancer [75]. A phase I clinical trial for CAR T-cell therapy in patients with HER2-positive cancer and recurrent brain or leptomeningeal metastases is currently underway, with doses administered intraventricularly (NCT03696030).

Limitations and Future Directions for CAR T-Cell Therapy

Other trials conducted in patients with glioblastoma have also demonstrated the capacity for adaptive resistance and recurrence of tumors [76] and cerebral edema remains a serious concern because of endothelial dysfunction and blood-brain–barrier permeability in patients receiving CAR T-cell therapy [77]. These observations pose serious challenges in the treatment of brain metastases using CAR T-cell therapy. However, investigations are underway that are attempting to gain a better understanding of these mechanisms and determine how to improve efficacy and reduce side effects of CAR T-cell therapy for brain tumors given the successes that have been achieved for hematologic malignancies. Current trials investigating combinations of immune checkpoint inhibitors targeting PD-1 or PD-L1 with CAR T-cell therapy targeting CD19 (NCT02926833, NCT02650999, and NCT02706405) may also provide additional clues.

Future directions for CAR T-cell therapy include identification of more tumor-specific targets [78], development of "off-the-shelf" or "universal" CAR T cells that are not autologous, or derived from the treated patient, and clustered regularly interspaced short palindromic repeats-CRISPR associated protein 9 (CRISPR-Cas9) mediated genome editing to enhance CAR T-cell trafficking and function [79–82]. These advances may overcome some of the barriers faced by the immune system in targeting tumor cells within the brain tumor microenvironment. Solutions to limit the harmful side effects observed in CAR T-cell therapy have also been proposed, such as rituximab, a widely used chimeric monoclonal antibody, and the inducible-caspase 9 system (iCasp9), which can act as a "safety switch" by triggering apoptosis of CAR T cells [83, 84], but nevertheless off-target toxicity remains a major challenge in targeting solid tumors overall. If able to overcome these challenges, CAR T-cell therapy may prove to be able to provide parallel results to those seen in hematologic malignancies and serve as a reasonable treatment for patients with brain metastases.

Oncolytic Viruses

Oncolytic viruses are engineered to discriminately target cancer by selectively replicating within tumor cells, causing them to lyse in the process. These immunotherapeutic approaches have demonstrated efficacy against intracranial tumors [85–88] showing that this therapy may also prove successful in the treatment of metastatic brain lesions. The idea of engineering viruses to specifically target tumor cells first began in the 1960s [89], and the knowledge and tools necessary to design oncolytic viruses were further refined in the following decades. Studies evaluating oncolytic viruses in the treatment of advanced stage cancer demonstrated improved clinical benefits, and in October 2015 the FDA approved the first oncolytic virus in the U.S. for the treatment of advanced stage melanoma [90]. It has been shown that the same mechanisms that allow tumor cells to rapidly grow within the tumor microenvironment—such as vascular permeability and proliferation, elevated metabolic activity, and apoptotic avoidance—also make them vulnerable to attenuated viral particles [91, 92], presenting a unique opportunity to target metastatic brain tumor cells. Clinically, oncolytic viruses function as antitumor therapeutics by directly lysing tumor cells as well as by promoting further antitumor immune responses. The general mechanism of oncolytic viruses is outlined in Figure 3.

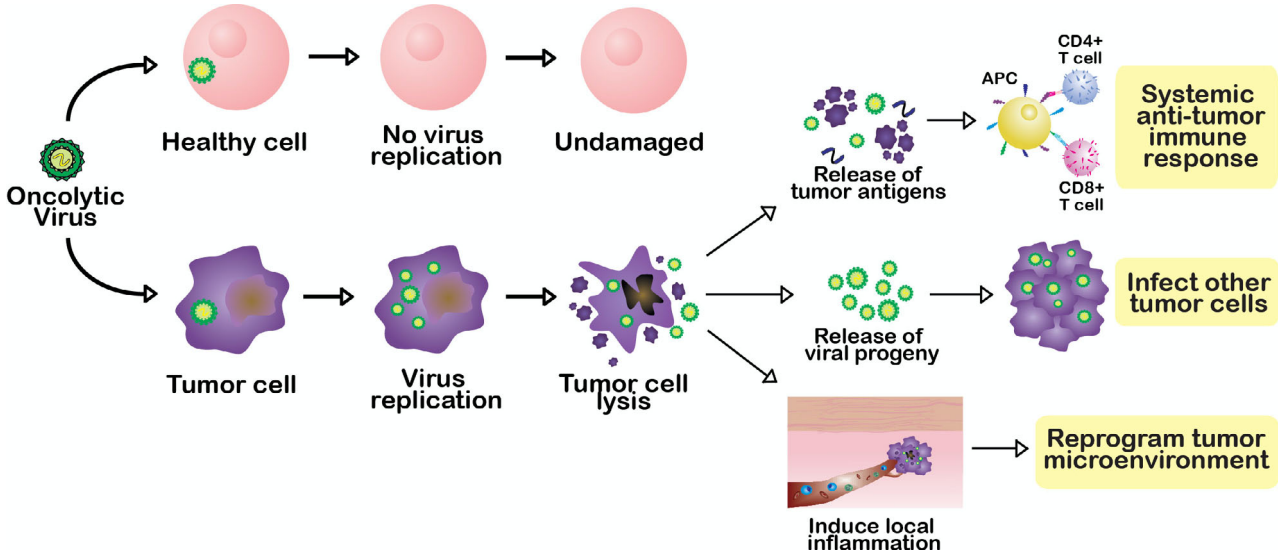

Figure 3. Mechanism of cancer immunotherapy using oncolytic viruses. Oncolytic viral therapy involves harnessing and reprogramming a virus to target tumor cells. The benefit of this therapy is the virus's ability to differentiate normal healthy cells from tumor cells. In normal cells, the modified virus cannot reproduce and is eliminated, sparing the healthy cell and avoiding widespread infection. The virus is either directly injected into tumor lesions or homes to tumors after intravenous or intraventricular injection. Once the tumor cell is "infected," it is then destroyed by oncolysis after viral replication and release, which triggers multiple antitumor processes: (a) release of viral and tumor particles that are then acquired by dendritic cells and presented to the host's T cells to instigate a systemic immune response; (b) release of new infectious viral particles to continue infection and oncolysis of remaining tumor cells; and (c) induction of local inflammation and reprogramming of the surrounding tumor microenvironment.
Abbreviation: APC, antigen-presenting cell.

Early Success of Oncology Viruses in Brain Tumors

Because of concerns that the blood-brain barrier would limit the ability of oncolytic viruses to directly interact with tumor cells, initial clinical trials in brain tumors involved infusion of agents directly into the tumor tissue or skull cavity [93, 94]. In 2018, Desjardins et al. published a study involving 61 patients with grade IV malignant glioma that received recombinant poliovirus and observed clinically significant outcomes in survival compared with historical controls highlighting how oncolytic viruses may be used in metastatic brain tumors [95]. That same year, Samson et al. also demonstrated that intravenous injections of reovirus serving as an oncolytic virus is able to successfully infect brain tumor cells by observing local infection for a small cohort in a phase I trial of nine patients, three of whom had metastatic brain tumors [96]. In addition, this study further demonstrated that reovirus upregulated the PD-1/PD-L1 axis and showed that PD-1 inhibition enhances systemic therapy in a preclinical model. Therefore, oncolytic viruses appear to be promising candidates for treatment of intracranial metastatic tumors and may improve the efficacy of immunotherapy by working in conjunction with immune checkpoint inhibitors.

Oncolytic viruses have also been shown to stimulate secretion of intermediary cytokines of PD-1 and PD-L1 expression as well as enhance T-cell infiltration in cancer tissues [97], thus further suggesting a potential synergistic mechanism for oncolytic viruses and checkpoint inhibitors against tumor cells. Although no current clinical trials are underway specifically for the treatment of brain metastasis using oncolytic viruses, studies using animal models are ongoing given that the combination of oncolytic viruses with immune checkpoint inhibitors warrants further exploration as a therapeutic strategy in immunotherapy.

Current Barriers

A number of limitations exist for the wide application of oncolytic viruses. One barrier has been the host's own immune system, which may clear oncolytic viruses and significantly reduce the total number reaching their target site for a successful clinical response [98]. Another has been the numerous ways in that brain metastases may evade immune responses and anticancer therapies, including their ability to rapidly proliferate and transform the tumor microenvironment. Appropriate dosing, delivery, and recognition of specific cellular targets are all additional factors that require further research before the potential of oncolytic viral therapy in the treatment of brain metastases can be fully appreciated.

Looking Ahead

With an early diagnosis, therapies as those described here may serve to induce improved clinical outcomes as metastatic brain tumors would have had less time to expand and evolve. One of the most promising advancements in cancer management is in its early detection using "liquid biopsy," which purports to diagnose cancer by measuring small amounts of tumor cells—or biomolecules derived from tumor cells, such as circulating tumor DNA (ctDNA)—in blood or other body fluids. ctDNA from patients with brain metastases can be detected in liquid biopsies taken from the cerebrospinal fluid (CSF) [99]. Successful genotyping of ctDNA found in the CSF of a patient with brain metastatic breast cancer undergoing treatment demonstrates the feasibility of this approach [100]. Studies have also shown that ctDNA from blood samples could be used to characterize and monitor some tumors that do not have CNS

involvement [101]. Its use in brain tumors has not shared the same success, however, because of the scarce levels of ctDNA detected in plasma for these patients [102].

The implications of successfully using liquid biopsies for brain metastases are notable, as they could allow for earlier diagnosis, and perhaps molecular profiling, of a brain lesion in order to initiate the most appropriate treatment. If treatment is warranted, liquid biopsy to measure cancer cells in CSF, in conjunction with systemic immunotherapy, may come to be a preventive strategy in clearing tumor cells in the CNS before they are visible on imaging or become symptomatic. For example, less aggressive therapy may be needed to achieve remission if metastatic disease is detected early. CAR T-cell therapy may also benefit from an earlier diagnosis as the immune response to eliminate metastatic brain tumor cells could be less aggressive if tumor burden is low [103, 104]. This could signal not only a potentially more efficacious treatment but one that may hold a lower side effect profile for all these modalities.

With our growing understanding of the tumor microenvironment, researchers have been able to identify novel ways to enhance the immune system and provide additional strategies toward the treatment of cancer, including brain metastases. Because of the short life expectancy of patients diagnosed with secondary brain tumors, the need for more effective therapy is critical. The advent of new immunotherapeutic strategies that have demonstrated efficacy in animal models and in early clinical trials may hold unfulfilled potential, as monotherapy or in combination, for patients suffering with metastatic brain cancer.

Although trials to date have largely included patients with previously untreated brain metastases, exploring the use of multiple treatments and their efficacy remains largely unexplored. Corticosteroids such as dexamethasone, the preferred agent because of its minimal mineralocorticoid effect, control intracerebral edema in metastatic brain tumors [105]. As steroids can theoretically abrogate the effects of immunotherapy, investigating how to best combine steroids with immunotherapy remains an important clinical question. Seizures are a common presentation of brain metastases because of local changes exhibited by the intracranial lesions [106]. Thus, understanding how different antiepileptic medications interact with the newer immunotherapies could be explored alongside novel immunotherapies [107]. Additionally, neurosurgical intervention and SRS remain appropriate treatments for individuals with limited intracranial lesions and controlled primary cancers [108]. Further research merging these different approaches and evaluating their combined efficacy is still needed.

Conclusion

At the moment, we only possess a rough mechanistic understanding of the efficacy of the modalities discussed in this review and an incomplete awareness of the potential adverse effects that may accompany these new immunotherapeutic strategies. We are also largely unaware of the intricate ways in which the immune system may interact with cancer cells to promote or contain proliferation. Besides evasion, components of the immune system may actively assist tumor growth and metastasis, such as in the disruption of the blood-CSF barrier [109]. Moving forward, as the role of immunotherapy in the treatment of brain metastatic cancer continues to expand, it will be important to consider how these therapies will guide clinical decisions for patients and providers in the age of precision medicine.

Author Contributions

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Disclosures

Ryan J. Sullivan: Amgen, Merck (RF), Array BioPharma, Amgen, Asana Biosciences, Bristol-Myers Squibb, Compugen, Genentech, Merck, Novartis, Iovance, Replimune (C/A); **Priscilla K. Brastianos:** Tesaro, Angiochem, Genentech-Roche, ElevateBio, Eli Lilly & Co. (C/A), Merck, Eli Lilly & Co., Bristol-Myers Squibb, Pfizer (RF), Merck, Genentech-Roche (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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